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Long term methylphenidate exposure and growth in children and adolescents with ADHD. A systematic review and meta-analysis.

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HIGHLIGHTS

- MPH is a very effective treatment for ADHD but there are concerns about potential adverse effects of extended treatment on several systems, including growth.
- Long term MPH appears to be associated with a statistically significant impact on height and weight in ADHD children and adolescents, but effect sizes are small, with possible minimal clinical effect.
- Sensitivity analysis did not reveal a significant effect of dose, age and drug naïvity condition as possible clinical moderators
- Data on effect on pubertal maturation, although limited, seem to favour the exclusion of a possible drug effect on sexual maturation in ADHD subjects.
- Current clinical practice guidelines indicate the need of a careful assessment of growth parameters before starting stimulant treatment and the periodic monitoring using standardised growth charts. Particular caution should be taken in pre-school children.

ABSTRACT

Background: Methylphenidate (MPH) is an efficacious treatment for ADHD but concerns have been raised about potential adverse effects of extended treatment on growth.

Objectives: To systematically review the literature, up to December 2018, conducting a meta-analysis of association of long-term (> six months) MPH exposure with height, weight and timing of puberty.

Results: Eighteen studies (ADHD n=4868) were included in the meta-analysis. MPH was associated with consistent statistically significant pre-post difference for both height (SMD = 0.27, 95% CI 0.16-0.38, $p < 0.0001$) and weight (SMD = 0.33, 95% CI 0.22-0.44, $p < 0.0001$) Z scores, with prominent impact on weight during the first 12 months and on height within the first 24-30 months. No significant effects of dose, formulation, age and drug-naïve condition as clinical moderators were found. Data on timing of puberty are currently limited.

Conclusions: Long-term treatment with MPH can result in reduction in height and weight. However, effect sizes are small with possible minimal clinical impact. Long-term prospective studies may help to clarify the underlying biological drivers and specific mediators and moderators.

KEY WORDS:

Attention deficit/hyperactivity disorder (ADHD); methylphenidate; stimulants; height; weight; growth; puberty.

1 INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders (Polanczyk et al., 2014). It is characterized by two main symptom dimensions, inattention and motor restlessness/impulsivity, which are pervasive and result in significant functional impairments (APA, 2013). According to international guidelines, treatment for ADHD should follow a multimodal approach that combines behavioural and pharmacological treatment (NICE, 2018; Pliszka, 2006; Taylor et al., 2004). The first-choice medication (Taylor et al., 2004) and the most frequently used treatment for ADHD in Europe is Methylphenidate (MPH). Positive effects of methylphenidate and other psychostimulants have been reported in numerous studies and meta-analyses, across a range of outcomes including core ADHD symptoms (Cortese et al., 2018; Coghill et al., 2017; Faraone & Buitelaar, 2010; Storebo et al., 2015). However, their use can be accompanied by a range of adverse effects including elevated blood pressure and heart rate (Hennissen et al., 2017), sleep disturbance, nervousness, reduced appetite, headache and abdominal pain.

Effects on growth are also prominent among these adverse effects. These include weight loss and height gain reduction occurring after extended use (Graham & Coghill 2008; Cortese et al., 2013; Storebo et al., 2018). Although many studies have measured the effects of clinical treatment with stimulant medications on growth and weight loss, there is as yet no clear consensus as to whether observed changes in growth are related specifically to stimulant medication or to other causes such as the condition of ADHD itself. Furthermore, the overall clinical significance of medication-related reductions in height during development has been questioned (Vitiello, 2008) – with researchers arguing that final adult height should be considered the ultimate index of growth for a correct evaluation (Jensen et al., 2004). The key question for these researchers is whether children treated with medication obtain their expected height as adults, or not (Swanson et al., 2017). Studies providing longitudinal data suggest that stimulants reduce growth in height by as much as 1 cm/year during the first three years of treatment and that this reduction can be clinically significant (Poulton, 2005). Some data suggest that these effects attenuate over time so that final adult stature is not affected by prior stimulant exposure (Faraone et al., 2008; Biederman et al., 2010; Kramer et al., 2000; Peyre et al., 2013). Finally, other authors reported that the height or weight changes might be a natural symptom of ADHD rather than a consequence of medication (Spencer et al., 1996; Hanc & Cieslik, 2008; Swanson et al., 2007). While, on average, reported effects of stimulants on growth appear to be modest, a substantial variability has been observed, with some children seemingly completely unaffected (Biederman et al., 2010; Findling et al., 2009; Zachor et al., 2006), whilst others experience significant growth suppression (Pliszka et al., 2006; Charach et al., 2006; Zhang et al., 2010; Poulton et al., 2012).

A recent publication by Swanson and the MTA Cooperative Group re-examined children's physical growth for cost-benefit evaluation and revealed that the "*New medicated subgroup"* was, at the 36 months follow up point, 3.04 cm shorter and 2.71 kg lighter than the "*Not medicated group*" with a growth-related cost persisting into adolescence and adulthood. During this last phase of observation, orthogonal comparisons revealed that treated cases were shorter than the untreated cases, indicating that height suppression was correlated to treatment (Swanson et al., 2018).

Earlier detailed reviews (Poulton et al., 2005; Faraone et al., 2008) substantially confirmed that treatment with stimulants (methylphenidate and amphetamine) in childhood, may reduce expected height and weight when only high quality studies are considered (longitudinal designs analysing changes in z-scores). Studies that failed to detect effects on growth were generally of poor methodological quality. All these reviews, although extensive and very well conducted, did not completely resolve the key issues related to the effects of MPH on growth. They concluded that more work was still needed in order to both clarify the effects of variations in formulation and dosing regime and better understand how individual characteristics moderate MPH effects. Thus, following the European Committee for Medicinal Products for Human Use (CHMP; 2009) requesting provision for further safety information about methylphenidate, specifically asking for more data on the long-term effects of MPH on growth and development in children and adolescents, we aimed to perform an update on the topic by exploring the recent most relevant published literature and by conducting a meta-analysis where data were adequate.

Compared to previous searches we aimed to specifically explore the effects of methylphenidate exposure on growth (excluding other stimulant medications when possible), by selecting a reasonable time of treatment exposure (> 6 months) for a mid and long term evaluation. As more than ten years have passed since the extensive review performed by Faraone et al. (2008) was published, our objective was to integrate new evidences of the last ten years with the hypothesis of including more studies with stronger methodologies. This could allow a more precise estimate of pooled effects to be made and an analysis of heterogeneity to be undertaken through sensitivity analyses in order to address the following questions:

- *Is MPH associated with clinically significant reduction in growth in children with ADHD?*
- *Are such effects moderated/predicted by patient's characteristics (baseline auxological parameters, age, gender)?*
- *Do dose and formulation (immediate release vs long acting), length of treatment, previous treatment history or continuous versus non-continuous therapy moderate the effect of MPH on growth?*
- *Does MPH affect the timing of puberty?*
- *Does MPH affect body composition and/or bone metabolism?*

2 METHODS

The systematic review was restricted to studies examining the effects of methylphenidate on growth in children and adolescents suffering from ADHD. There was no restriction with regards to ADHD subtype, presence of co-morbid disorders, gender, or socio-economic status of participants.

Since no long-term randomized clinical trials reporting standardized data on growth outcomes are available, for the purpose of this review all observational, open-label, retrospective and prospective study designs, with or without a control group were included.

2.1.1 INCLUSION AND EXCLUSION CRITERIA:

Studies were eligible for inclusion in a quantitative analysis if they:

- enrolled subjects with a diagnosis of ADHD formulated according to DSM criteria (DSM-III, DSM-III-R or DSM-IV) or of Hyperkinetic Disorder according to the previous ICD system;

- reported a continuous length of treatment of at least six months.

- examined subjects on MPH as a mono-therapy or associated with other stimulant medications when it was not possible to distinguish between the two drugs;

- were written in English;

- reported data on humans.

- Recorded growth parameters and/or data on pubertal maturation in children (≥ 6 and < 12 years) and/or adolescents (≥ 12 and < 18 years) exposed to MPH, using adequate population-based norms for height and weight.

Studies were excluded if:

- they were restricted only to the exposure of the drug in adulthood;

- the effects on growth were related exclusively to psycho-stimulants other than MPH;

- they reported data on animals

2.1.2 Outcome measures

Only studies clearly reporting Z scores for height and/or weight, expressed as mean and Standard Deviation (SD), baseline (pre) and at the endpoint (post), were included into the quantitative analysis. The outcome measures were the pre–post treatment change in height and weight Z scores related to MPH treatment. Where more than one follow-up measurement was performed within the same study, the outcomes of the longest follow-up were recorded in order to explore measurements of growth parameters over the longest follow-up interval. Where studies included auxological parameters from both MPH and a comparison arm (e.g., not medicated ADHD or typically developmental control group), only the parameters for the medication treatment group were included in the main analysis. A separate analysis was performed including Δ Standard Mean Difference (SMD) in order to compare the medicated and not medicated/non ADHD sample.

When data were available, we also reviewed the changes in body composition (lean tissue, fat masses, fat distribution, bone mineral density, bone turnover) and the onset of pubertal maturation.

2.2 SEARCH STRATEGY

We first searched for the most relevant published reviews on the topic (Faraone et al., 2008; Poulton et al., 2005; Ptacek et al., 2009, 2014; Rapport et al., 2002). In a second search we considered individual trials published from the 70s up to December 2018 and not included in the previous reviews, by using the following research sources (PubMed, MEDLINE via Ovid SP, EMBASE via Ovid SP, PsycINFO via Ovid SP).

The search strategy involved medical subject headings [MeSH] and terms as free text word (see appendix 1 including a flow chart of the search strategy).

Articles were all screened by two of the authors (SC, CB) on the basis of title and abstract. Assessment of articles for final inclusion was based on full text review. Discrepancies were resolved by consensus between the two authors and, in case of disagreement, a third author (AZ) acted as arbitrator.

From each paper the following data were extracted into an Excel file:

- Characteristics of the studies: year of publication, location, study design, sample size, diagnostic criteria;
- Characteristics of study participants: sex distribution, mean and range of age, number of growth data information, whether ADHD were medication naïve at baseline or previously exposed to ADHD medications;
- Characteristics of medication: mean and range doses, formulation, length and continuity of treatment;
- Primary and secondary outcome measurement and time of outcome measurements.

2.2.1 Data analysis

A quantitative analysis was conducted for those studies which clearly reported Z scores for height and/or weight expressed as mean and SD at baseline and after methylphenidate treatment. The outcome of the latest follow-up was recorded. A pre–post within-group design was used to meta-analyse medication effects on height and weight. Data were analysed using RevMan 5.3 (http://ims.cochrane.org.revman). Given the heterogeneity of sample characteristics and design in the included studies, individual effect sizes (ES) were calculated by using a random effects model and expressed as SMD with 95% confidence intervals. ES of about 0.3 represents a small effect, while an ES of about 0.5 or 0.8 indicate respectively a medium and large effect (Cohen, 1977)..Heterogeneity was assessed using the I^2 test.

3 RESULTS

Tables I and II summarise the main information of the 18 studies included in the quantitative analysis of this systematic review.

3.1 CHARACTERISTICS OF THE STUDIES INCLUDED

Included studies were conducted between 1976 and 2016 with publication years ranging between 2003 and 2018.

Seven studies were performed in the USA, three were from Australia (Poulton & Cowell 2003; Poulton et al., 2012; 2016), one each from Canada (Charach et al., 2006), Spain (Durà-Travè et al., 2012), Turkey (Bereket et al., 2005), Italy (Germinario et al., 2013), Sweden (Landgren et al., 2017), Denmark (Powell et al., 2015) and Brasil (Granato et al., 2018). Five studies were multicentre (Spencer et al., 2006; Faraone et al., 2007; Swanson et al., 2007; Lisska et al., 2003; Germinario et al., 2013) with a number of sites ranging between 2 and 87. All multi-site studies were conducted in USA apart from Germinario et al., that was conducted in Italy.

The selected studies include a total of 4868 children and adolescents with ADHD (range= 34-1758; mean= 270.44; SD= 396.60; median = 156); around 80% of included participants were male; 3268 of them received, at least at a certain point, MPH treatment. Adequate data on the impact of MPH on growth and development were available for 2570 subjects (range= 24-410; mean = 142.77; SD = 128.19; median= 88).

Age of subjects at the beginning of treatment was between 3 and 17 years (mean age 8.79, SD = 1.34). Nine studies were limited to pre-adolescent participants (<13 years, mean age= 8.53, DS= 0.80), while the rest of the studies examined both children and adolescents up to 18 years of age.

Only three studies considered pubertal stage (Tanner & Whitehouse, 1976). Bereket et al., (2005) specified that they only included pre-pubertal participants. Zachor et al. (2006), used a simplified method to define the pre-pubertal stage (age range between 4.5 and 8.5 years to assure that both genders could be included); Diez-Suarez et al. (2017) as well, used a simplified method by dividing the sample into children (age range between 6 and 12 years) and adolescents (between 13 and 18 years).

3.1.1 Study Designs and follow up

All the included studies were observational; 9 were defined as retrospective (based on reviews of clinical records), one was designated as partially retrospective combining data from clinical records and from longitudinal follow up. Eight were prospective.

Duration of follow-up and mean duration of medication treatment ranged between a minimum of 21 months and a maximum of over 72 months (mean: 37.56 months; SD 13.83; median 36).

Eight of the 18 studies included a control sample: in all 1624 subjects (range = 35-394; mean= 232; DS= 133.99; median = 260) including either ADHD subjects (n = 360) or non-ADHD comparisons (n = 1264) or both. Majority of the studies (Harstad et al., 2014; Poulton et al., 2012; 2016; Swanson et al., 2007; Lisska et al., 2003; Swanson et al., 2017; Granato et al., 2018) included typically neurodevelopmental children as controls, however only three of them reported data for a longitudinal comparison (Swanson et al., 2007; Lisska et al., 2003; Poulton et al., 2016), while group comparison data where mostly limited only to a single observation at baseline in the other studies. Effects of methylphenidate were, in one case compared to amphetamines (Pliszka et al., 2006), or, in another case, to atomoxetine (Germinario et al., 2013).

Ten studies selected only initially drug naive patients (Bekeret et al., 2005; Charach et al., 2006; Germinario et al., 2013; Lisska et al., 2003; Poulton et al., 2012; Poulton &Cowell 2003; Diez-Suarez et al., 2017; Powell et al., 2015; Poulton et al., 2016, Granato et al., 2018), while other 7 included mixed populations that included both drug naive and previously treated patients.

Within the selected 18 studies, the MTA was initially designed as a 14-month randomized clinical trial (RCT) to test hypotheses about four treatment strategies in 579 ADHD children aged 7-9.9 years: medication management (Med), behavior modification (Beh), their combination (Comb), or treatment-as-usual in a community comparison (CC). After the RCT phase, the MTA transitioned into an observational long-term follow-up (LTF) phase, during which medication use was monitored prospectively in terms of patterns of stimulant medication during follow up time as *non-medicated, newly medicated, consistently medicated and inconsistently medicated* (Swanson et al., 2007; Greenfield et al., 2014) or-long-term patterns of prospective treatment with medication from childhood through adolescence: *Consistent, Inconsistent,* and *Negligible* (Swanson et al., 2017).

3.1.2 Medication and therapeutic dosages

Eight studies examined methylphenidate (MPH) together with other stimulants (amphetamine). One of them (Pliszka et al., 2006) compared a sample of subjects continuously treated with MPH for at least one year with a sample treated with amphetamines. The other ten specifically examined the effect of MPH but included different formulations: seven examined immediate and/or modified release formulations, one a trans-dermic patch (Faraone et al., 2007), while the other two studies did not specify the formulation (Granato et al., 2018; Lisska et al., 2003). Dosages were specified in different ways, but mainly as mean daily dose; two studies did not specify the dose. Average daily doses varied considerably between studies from 0.48±0.22 mg/kg/day (Germinario et al., 2013) to 1.31±0.2 mg/kg/day (Durà Travè et al., 2012). Daily average dosages of MPH varied from 6 to 85 mg/day, with a mean daily dose of around 29.93 ± 12.14 mg/day. The study examining the effect of trans-dermic MPH delivery reported a time of daily exposures to treatment of between 9 and 12 hours/day (Faraone et al., 2007).

3.1.3 Primary outcome measures

The primary outcome measures varied across studies and were somewhat dependent on the period during which the study was conducted. On the basis of our criteria, we were able to include only recent studies that expressed the variations in height, weight and BMI through standardized age and gender normed z-score parameters.

Two studies also included the height velocity-SDS as a *primary outcome* measure (Lisska & Rivkees, 2003; Poulton & Cowell, 2003). In addition to more standardised measures, one study (Poulton et al., 2012) reported changes in body composition (lean tissue, fat masses, fat distribution, bone mineral density) using the Dual-energy X-ray absorptiometry (DEXA) scans.

3.2 QUANTITATIVE ANALYSIS

Question 1*. Is MPH associated with clinically significant reduction in growth in children with ADHD?*

3.2.1 PRE–POST WITHIN-GROUP DESIGN ANALYSES

Eighteen studies for height (Figure 1) and fourteen studies for weight (Figure 2) met inclusion criteria for a quantitative meta-analysis. For both height and weight, all but four studies (Diez-Suarez et al., 2017; Harstad et al., 2014; Landgren et al., 2017; Bereket et al., 2005) reported data on multiple measurements (with a minimum of 2 to a maximum of 6 different measures). For studies including multiple follow-up times, outcome measures were considered at the latest follow up time, varying from a minimum of 21 to a maximum of 72 months. Stimulant therapy (methylphenidate and amphetamine, when it was not possible to distinguish between the two) was associated with a small, however statistically significant pre-post difference both for height (SMD = 0.27, 95% CI 0.16-0.38, p <0.0001; Figure 1) and weight Z scores, (SMD = 0.33, 95% CI 0.22-0.44, p <0.0001; Figure 2) with a similar large between trial heterogeneity (respectively I^2= 52% and 44%).

We also performed a subset of analyses including the studies reporting data at these two specific follow-up points: 12-18 months and 24-30 months.
A moderately significant pre-post difference for weight Z scores, was found when data were examined at the 12-18 month follow up (SMD = 0.46, 95% CI 0.29-0.62, p <0.0001; Figure 3). The largest impact of MPH on weight was usually reported at the end of the first 6 months (Poulton et al., 2012; Poulton et al., 2016) and in general within the first 18 -24 months of treatment (Poulton & Cowell 2003; Zachor et al., 2006) with a plateau at subsequent follow-up measures (Powell et al., 2015).

In terms of height, the most significant pre-post difference, was found when examining data at the 24-30 month follow up. These results confirmed the association with a small but highly statistically significant pre-post difference for height Z score comparable to the one found at the last recorded follow up (SMD = 0.27, 95% CI 0.22-0.31, p <0.0001; Figure 4).

Three studies reported an impact during the first 6-12 months of treatment with a subsequent normalization thereafter (Faraone et al., 2007; Poulton et al., 2012; Poulton et al., 2016). Three other studies showed an impact on height later in treatment (Poulton & Cowell, 2003), after 12 (Germinario et al., 2013) or even 24 months (Durà-Travè et al., 2012). Poulton and

Cowell (2003) reported a normalization of growth within 30-42 months. In a recent work it was confirmed that the decline in Z-height growth over time plateaued from 12–47 months, though without reaching baseline, but remaining within the expected range for age (Powell et al., 2015). Results at the 3 year follow-up of the MTA study confirmed a suppressive effect on growth during the first two years of treatment, but suggested that this effect on growth is still observable after three years (Swanson et al., 2007).

3.2.2 Analysis of controlled trials

As stated before, only three studies reported data for a longitudinal comparison of height with a control population: not medicated ADHD subjects (Swanson et al., 2007) and typically developing siblings (Lisska et al., 2003; Poulton et al., 2016); only two studies reported data for weight. In these cases stimulant therapy (methylphenidate and amphetamine) was associated with a moderate, statistically significant difference for weight (SMD = -0.47, 95% CI -0.75, -0.19, p =0.0010; I^2= 0%, Figure 5) but not for height Z scores, (SMD = -0.84, 95% CI -1.72, 0.05, p = 0.06, I^2=93, Figure 6).

3.3 MODERATORS OF THE TREATMENT EFFECT

Question 2 and 3. *Do patient (baseline auxological parameters, age, gender) and medication characteristics (dose, formulation, length of treatment, drug naïve condition) moderate the effect of MPH on growth?*

A set of sensitivity analyses was performed to assess the effect of possible clinical modifiers (MPH as monotherapy, formulation, dose, age, the drug naïve condition) and the effect of the study design (retrospective vs prospective). Figure A and Table A.

Ten studies for height (figure 7) and seven for weight (figure 8) examined the effects of MPH as a **monotherapy** confirming the previous results evidencing a small, but statistically significant pre-post difference both for height and weight Z-scores. SMD for height was = 0.23, 95% CI 0.08-0.38, p=0.003; I^2=62 while SMD for weight was = 0.24, 95% CI 0.14-0.35, p<0.0001; I^2=10.

The four studies examining the MPH **long-acting formulations** (Dura'-Travè et al., 2012; Faraone et al., 2007; Landgren et al., 2017; Spencer et al., 2006) confirmed a similar pre-post difference for weight Z scores (SMD = 0.32, 95% CI 0.18-0.46, p <0.0001; I^2 =56), while the effect on standardized values for height resulted slightly smaller with a higher heterogeneity between trials (SMD = 0.09, 95% CI 0.03-0.16, p =0.006; I^2 =68).

Sensitivity analysis did not reveal a significant effect of **dose** on either height or weight mean Z scores when considering a mean MPH daily dose of < 30 mg/day vs ≥ 30 mg/day. However it is worth noting that some studies evidenced a dose effect by regression models. Charach et al. (2006) reported an effect on height for patients treated with doses out of the usual clinical range (≥2.5/mg/kg/day) at their 48-month follow-up visit. The MTA study confirmed these last results: showing an effect on growth closely related to the dose (Swanson et al., 2007). Powell et al., (2015) reported a stronger dose effect, particularly for weight, in patients treated with doses ≥ 1.5/mg/kg/day even after 72 months. The studies by Poulton et al., showed a dose-related effect to height velocity within the oldest subject group (14-16 years; Poulton et al., 2013) and a larger effect on height and weight for larger doses (Poulton et al., 2016). Interestingly, 2 of the studies reporting a negative impact of stimulants on height did not find any correlation with dose (Zhang et al., 2010; Dura'-Travè et al., 2012). Two more trials reported a possible correlation between dose and the impact on weight but not height (Faraone et al., 2007; Landgren et al., 2017).

No significant effects were found for **age** (children <12) or the **drug naïve condition.**

Sensitivity analysis did not reveal a significant effect of **study design** either. A similar pre-post difference for height Z scores was found when including only studies with a prospective design (SMD = 0.25, 95% CI 0.09-0.40, p=0.002; I^2 =26) or with a retrospective design (SMD = 0.28, 95% CI 0.13-0.44, p=0.003; I^2 =63), as well as for weight Z scores (SMD = 0.34, 95% CI 0.20-0.48, p <0.0001; I^2 =0) when including studies with a prospective design compared to the retrospective ones (SMD = 0.32, 95% CI 0.14-0.49, p p=0.003; I^2 =61).

3.4 GROWTH ADVERSE EFFECTS ON INDIVIDUAL LEVEL

Considering the importance of possible clinical effects at individual level in clinical practice, we also evaluated the available single patient data in terms of appetite suppression, weight loss, deviation or decreasing from expected Z scores values and medication cessation.
Only a minority of studies (5/18; 27.7%) reported individual level data about stimulants adverse effects on appetite and growth (either effects on height or weight). The most prevalent adverse effect was appetite suppression. Zachor et al., 2006 (n=81) reported that 54

subjects (about 60%) presented with this effect, but only 10 subjects changed medication due to this adverse effect.

Landgren et al., (2017) evidenced that 28 out of 69 (41%) individuals deviated and decreased from their expected height Z score values at least 0.5 SD during the treatment period. The treatment effect on height development on a group level was minimal, about -0.2 SD (subjects with the greater decrease between baseline and follow up were on average taller at baseline), but the group of children with height <1.5 SD increased from 5% (5 subjects) to 10% (8 subjects). In the study by Granato et al., (2018) 3 individuals overall (3.2%) became thin, with a minimum weight Z score of −2.81.

In two patients there were sufficient concerns about growth rates to recommend cessation of medication (Poulton et al., 2003) while another subject ceased medication for appetite suppression associated to insomnia, tics and headache (Poulton et al., 2016).

3.5 Effect of MPH on puberty

Question 4. *Does MPH affect the timing of puberty?*

Data is currently limited on the impact of either ADHD or MPH on the timing of puberty. Using a questionnaire for self-staging of pubertal maturation, Spencer et al. (1996) did not detect any obvious influence of methylphenidate in 124 boys with ADHD, the most of them treated with stimulant medication. A comparable study of 124 girls with ADHD and a matched control group also found no evidence for an influence of MPH on pubertal development in girls with ADHD (Biederman et al., 2003). Unfortunately, no information on duration of treatment with stimulant medication was reported for this sample, leaving open the possibility that the girls had not been treated long enough for either their growth or pubertal development to be affected.

A recent publication from the MTA found no evidence to suggest that stimulant medications significantly impacted the timing of puberty. Within this study a subset of participants with ADHD (n = 342) and a control group without ADHD (n = 159) completed self-report Tanner staging at the 36-month follow-up assessment. Further comparisons were made for the participants in the ADHD group who were *always* (n = 61), *never* (n = 56), *newly* (n = 74) and *inconsistently* (n = 116) medicated with stimulants. No statistically significant differences in Tanner stages of pubertal development were found between the ADHD and non-ADHD groups at the age of assessment (between 10 and 14 years of age) or among the ADHD medication subgroups (Greenfield et al., 2014).

Poulton et al. (2013) did report a delay in pubertal maturation for 14 to 16-year-old adolescents after three years of continuous treatment with stimulant medication. Of the 65 boys (age range 12.0-15.9) recruited for the study, the 22 aged 14.0-15.9 years reported significantly less advancement in their pubertal development compared to controls with no significant correlation with the dose of medication. No significant difference in the stage of puberty was found at 12.0-13.9 years of age. These findings suggest that stimulant medication may delay the rate of maturation during puberty but not the onset of puberty. However, the very small sample sizes limit the generalizability and replication in larger groups is required.

3.6 EFFECT OF MPH ON BODY COMPOSITION AND METABOLISM

Question 5. *Does MPH affect body composition and/or bone metabolism?*

Only two trials investigated bone mineral density and bone turnover as an index of changes in body composition related to stimulant medication. These reported contrasting results.

The pilot study conducted by Lahat et al. (2000) compared 10 ADHD subjects treated with MPH for 12 to 24 months (mean 13 ± 4) with 10 controls. Laboratory data and bone mineral density did not differ between the two groups and no child deviated from his height percentile during the treatment period.

The prospective study of Poulton et al. (2012) examined 34 children aged 4.7-9.1 years, newly diagnosed with ADHD and treated with dexamphetamine or methylphenidate. This group found significant reductions over 3 years in sex and height corrected Z scores for bone mineral content and bone mineral density compared to data gathered from 241 healthy children.

In a later publication Poulton et al., (2016) examined bone age over the first 3 years of treatment (dexamphetamine or methylphenidate) in ADHD children compared with their healthy siblings (controls). There were no significant growth differences between the two groups at baseline. The ADHD patients (n=40) showed no significant maturational delay compared to the 22 children belonging to the control group (RUS score: 49 U/year, 95% CI: 44–55, vs. 55 U/year, 95% CI: 47–63, P = 0.27). A subgroup of patients underwent serial biochemistry and dual-energy X-ray absorptiometry, recording a significant reduction in fat (5.61 ± 3.56–4.22 ± 3.09 kg, $P < 0.001$) and leptin (3.88 ± 2.87–2.57 ± 1.94 ng/ml, $P = 0.017$). No medication effect was found on the rate of maturation, which was mostly predicted by baseline leptin levels.

4 DISCUSSION

ADHD is a chronic condition frequently persisting during late adolescence and adulthood (Kooij et al., 2005). As current recommendations are to continue treatment for as long as it is needed and helpful (NICE, 2018), patients can, in theory, receive a pharmacological treatment for many years with consequent concerns related to potential long-term risks.

The findings of this review suggest that long term MPH use is associated, at the group level, with relatively minor impacts on height and weight in ADHD children and adolescents (pre-post difference for height Z score: SMD = 0.27 and weight Z score: SMD = 0.35). These estimates suggest that stimulants, at a therapeutically daily dose varying between studies from 0.48±0.22 mg/kg/day (Germinario et al., 2013) to 1.31±0.2 mg/kg/day (Durà Travè et al., 2012) and a mean daily dose of around 29.93 ± 12.14 mg/day, could slow height gain by approximately 1.39 cm and weight gain by approximately 1.96 kg for a 10-year-old boy over a 2-year period. When considering MPH as a monotherapy (pre-post difference for height Z score: SMD = 0.23 and weight Z score: SMD = 0.24) the growth gain decrease can be estimated around 1.25 cm less for height and 1.43 kg less for weight for the same 10-year-old boy. Over a 2-year-period, MPH could diminish gains in height by 1.65 cm and by 2.6 kg in weight for a 14-year-old boy. These effects however seem to be limited in time with a subsequent normalization (Poulton & Cowell, 2005; Faraone et al., 2007; Zhang et al., 2010; Poulton et al., 2012; Kim et al., 2014, Poulton et al., 2016) and for most individuals are likely to have minimal clinical or personal significance. Whether these changes are of concern would depend substantially on the individual child stature, as gaining 1,5 cm less could have a clinically significant impact only for subject with a height Z score < 2 DS at baseline. According to the studies reporting individual data, losses in expected growth were not considered clinically significant enough to stop treatment apart from two subjects (Poulton et al., 2003). Physicians generally did not advice to discontinue medication, underscoring the suggestion that stimulant associated deficits in growth did not pass a threshold that would be considered clinically significant. Subjects with the larger impact between baseline and follow up were on average taller at baseline, while the percentage of subjects who were considered very short or very light, tended to increase in a minimal part (<10%) from baseline to the last observation (Landgren et al., 2017).

The extremely heterogeneous nature of the included studies, and the many methodological limitations of the currently published papers on this topic, do however limit our ability to draw firm conclusions. One of the main methodological limitations in analysing MPH effects on growth relates to the definition of outcomes; for this reason we included only recent studies preferably expressing the variations in height, weight and BMI through standardized age and gender normed Z-score parameters. Methods of outcome measures were in fact an issue for earlier studies, particularly those published before the mid-90s. Most of these studies considered means of absolute weight and height as the primary outcome with only a few using the more standardised measures of percentiles calculated from standardized growth charts. Percentiles are still associated with significant imprecision since the averaging of percentiles tends to overemphasize the small differences near the mean and underestimate similar differences at the extremes (Spencer et al., 1996). More recent publications have generally considered Z scores for height, weight and height velocity as primary outcomes. These measures are clearly superior to the previous ones: they allow for more valid comparisons as they correct for age and sex, avoid mathematical distortions, and show similar sensitivity to change at all levels of the curve.

When used with country specific norms, Z scores can also account for geographic and ethnic variability. They are however dependent on accurate population norms. This can be an issue for many countries, including some of those used in the US, where much of the research has been conducted, using norms that can be out of date and do not account for the secular changes in growth measured in the general population over time (www.cdc.gov/growcharts). Despite the use of more appropriate outcome measures in recent studies and considering the controversial results of the studies of the seventies and the eighties, it is somewhat surprising that relatively few long-term studies have been carried out in the last years and that many of those that have been conducted are affected by significant methodological limitations, precluding an accurate quantitative comparison.

A further important methodological limitation relates to the statistical management of the age of the participants. Since height does not vary linearly with age, the wider the age range of the sample being studied, the more vulnerable are direct comparisons of averaged height measurements to produce spurious results (Chinchilli et al., 1990). It is also important to notice that growth, and height in particular, can be described as a wave motion with a six-month periodicity. As a consequence it is generally agreed that at least 4 measurements of height, taken six months apart are required to reduce the potential for error when assessing growth status.

A more narrow definition of age of participants within the studies is however not enough to get more reliable results. In the majority of the studies included, the mean age at enrolment is about 10 years suggesting that many of those included will have been in puberty: during this time of development the height velocity increases most and is also the most variable, as the timing of puberty varies considerably between otherwise similar individuals. It would therefore be most appropriate to stratify the population according to specific stage of pubertal status as well as age. Alternatively, the analysis could be performed after excluding those subjects who were within puberty. This would however result in the loss of a considerable amount of data and leave a considerable hole in our understanding. Since most studies included all patients regardless of their pubertal status in their analyses, and none of the study actually assessed pubertal status independently of age, this may have diminished the power to detect an impact of MPH on growth. It is also important to notice that most studies included a male population (about 80% of the sample in the meta-analysis) preventing a clear comparison with the opposite gender and partially confounding the accuracy of data when the male and female populations were analysed together, considering the different pubertal maturation onset of the two genders.

The conclusions from our review should be therefore examined by considering the above mentioned limitations in the field and the methodological limitations of our approach. The poor quality of the studies limited the possibility to make direct between-study comparisons. Most studies did not have a control group and failed to report important information on individual data, including the effects of dropouts and previous treatment, or the rating of clinical significance of growth effects by physicians, parents, or patients. Other possible mediators as prenatal factors, such as toxic exposures, hereditary influences or ethnic and socio-demographic composition of their samples were generally not described. Our statistical analyses have therefore limited power due to the number of studies available for analysis.

The mechanisms by which stimulants may affect growth are not completely understood. Growth suppression in ADHD children can be a consequence of decreased appetite and reduction in caloric intake (Cortese et al., 2013; Ptacek et al., 2014; Vitiello, 2008), endocrinological or dietary factors (Ptacek et al., 2009) or could be caused by the dopaminergic effect of stimulants with the acute inhibition of growth hormone (De Zegher et al., 1993). Another possible mechanism is the effect of stimulants on slowing the growth of cartilaginous tissue and consequently the bone growth (Kilgore et al., 1979), with possible osteopenic effects for stimulants users (Howard et al., 2017).

When discussing the long-term effects, it is important to consider that changes, although with a generally minimal clinical impact, can vary on an individual basis. Higher baseline weight and height are often associated with a greater impact by stimulant medication, with the strongest correlation for weight (Safer et al., 1973; Mattes & Gittelman, 1983; Spencer et al., 1992; Zeiner et al., 1995; Scherts et al., 1996; Sund & Zeiner 2002; Zachor et al., 2006; Faraone et al., 2007) indicating that basal auxological characteristics may represent an important clinical correlate. Spencer et al., (2006) divided the sample by using Z scores quartiles for weight and height and confirmed a stronger effect for tallest and heavier children. Despite data suggesting that overweight and taller children may be more sensible to medication effects, a finding that could be seen as reassuring to patients of smaller stature, from a clinical point of view it remains important to remember that effects need to be measured at an individual level for individual patients.

Time of follow-up represents another important variable, when evaluating the possible impact of stimulants on growth: medication effects tend to attenuate over time both for weight and height. According to the results of previous reviews (Poulton et al., 2005; Vitiello, 2008), effects on height would manifest later in time with respect to weight (Faraone et al., 2007; Spencer et al., 2006; Lisska & Rivkees, 2003), with a similar trend of generally remitting in time (Poulton & Cowell, 2003; Klein & Manuzza, 1988; Safer et al., 1973), and time of follow up appears to be influenced by the condition of drug-naïvity at the beginning of the study. Drug naïve subjects have been shown to present a greater weight and BMI loss with MPH transdermal delivery system (Faraone et al., 2007). This characteristic pattern and the possible normalization of the auxological parameters over time may explain the negative results deriving from the studies including subjects already on stimulants and not drug naïve patients (Pliszka et al., 2006). The recent study by Powell et al. (2015) confirms this trend, with a temporary lag halt in growth and a Z height growth plateau after 12-47 months of follow up in a population of 410 drug-naïve ADHD subjects.

Although our sensitivity analysis did not reveal an effect for dose when setting the limit of a MPH dosage $<$ vs $\geq$ 30 mg/day, it is important to evidence that several studies have shown that, in a minority of patients treated with doses higher than usual, these dosages could be more predictive of height deficits (Charach et al., 2006; Lisska & Rivkees, 2003; Pliszka et al., 2006; Faraone et al., 2007; Poulton et al. 2013; Powell et al., 2015; Diez-Suarez et al., 2017; Poulton et al., 2016). In the Preschool ADHD Treatment Study (PATS study; Swanson et al., 2006), preschool children receiving prolonged treatment (n= 95), showed a yearly height deficit of about 20% (-1.38 cm / year) and a weight deficit of about 55% (-1.32 Kg / year) than expected, regardless of the administered dose (mean dose 14 mg/day). This finding could be explained by the young age of the sample evidencing a possible higher sensitivity to MPH according to the age range of patients, with particular attention to the younger children.

Safety findings on growth parameters from a recent open-label 2-year lisdexamfetamine dimesylate trial in ADHD subjects aged 6–17 years (N=314) appear consistent with previous studies of stimulant medications (Banaschewski et al., 2018). Mean weight, height and body mass index Z-scores transiently decreased over the first 36 weeks of the study and then stabilised, with no evidence of delayed onset of puberty.

In order to minimize growth adverse events, one of the recommended strategies by clinical guidelines (NICE, 2018; Taylor et al., 2004), is to plan a break from medication, referred as a “drug holiday” (van de Loo- Neus, Rommelse, & Buitelaar, 2011; Ibrahim et al., 2015).

A recent comprehensive search of the literature identified 22 studies published from 1972 to 2013 with the aim to map the experience of drug holidays from ADHD medication. The authors found evidence for a positive impact on child growth with longer breaks from medication, and shorter breaks could reduce insomnia and improve appetite (Ibrahim & Donyai 2015). While older studies suggested that withdrawal or interruption of treatment may attenuate the suppressive effect of stimulants on growth due to a rebound phenomenon (Safer et al., 1972), with significant effects both on height (Klein et al., 1988) and weight (Satterfield et al., 1979), more recent studies, on the other hand, do not support the hypothesis of a rebound effect of growth after suspension of treatment or did not confirm a positive correlation with "drug holiday" (Pliszka et al., 2006; Spencer et al., 2006; Lisska & Rivkees, 2003; Poulton et al., 2003; Vitiello et al ., 2008).

The discrepancy between these results can potentially be reconciled when one takes into account that those studies that reported correlations often examined together both drug naïve and subjects on treatment from a long time. On the other hand, the studies that did not find a correlation often did not control the drug holiday in detail, leaving it to the parents to decide when and how to have drug holidays, without a distinction in terms of length of therapeutic suspension (weeks vs. months).

The ultimate index of growth is whether or not an individual reaches their target height (expected height as an adult); however none of the selected longitudinal studies included the reaching of target height (estimated as a genetic variable taking into account parental height) at the end of development as the main outcome. The majority of studies in adult patients treated with psychostimulants as children suggest that final height may not be significantly impaired, although, in the light of more recent publications (Swanson et al., 2017), this hypothesis still remains uncertain and requires further investigation. Biederman et al. (2010) in their case-control study with a ten-year follow up, did not find any evidence that stimulant treatment could affect final adult height in a sample with a mean age about 21 years. A recent search from the National Epidemiologic survey on Alcohol and Related Conditions (NESARC) data collected in 2004-2005, confirmed the absence of any significant difference in the final adult height in ADHD subjects treated with stimulants during the developmental age (n = 216), compared to ADHD never treated with stimulants (n=591) and a control sample (n = 34652; Peyre et al., 2013). This finding was further confirmed in a recent longitudinal study comparing 243 ADHD to 394 controls. No statistically significant differences in adult height were found between the two groups (Harstad et al., 2014).

The recent publication of MTA outcomes in early adulthood (25 years of age; Swanson et al., 2017) however contradicts the previous findings, with the ADHD group reported to be 1.29 ± 0.55 cm shorter than the control group and showing a higher impact on height for subjects constantly treated compared to the ADHD sample discontinuing medication. This discrepancy of findings of MTA with the other studies appears to be related to changes in the clinical use of medication and differences in the cumulative dose, to the adequate separation of treated and untreated ADHD subjects and to the average age of treatment initiation.

All this information should be however read in the context of different potential confounding factors including epigenetics (i.e. low birth weight of the child and of their parents and grandparents), the positive secular trend of growth, the progression age of menarche and a possible genetic condition known as constitutional delay of growth and puberty (CDGP, Howard 2018). This is a relatively frequent condition (2-3% of children), generally self limited and representing the extreme end of normal pubertal timing, and the commonest cause of delayed puberty in both boys and girls associated with adverse health outcomes including short stature, reduced bone mineral density and compromised psychosocial health (Zhu and Chan, 2016). At the moment it would be very costly to genetically examine all methylphenidate-treated patients to exclude such possible confounding variables. However, future progress in gene discovery and technical developments may facilitate the availability of genetic diagnosis as part of clinical care for patients on a pharmacological treatment and a possible condition of self-limiting delay puberty. At the moment, studies using a self-controlled case series design could be useful in giving more information about data at an individual level, in order to obtain more precise indication for clinical practice for the management of possibly more vulnerable subjects.

5 CONCLUSIONS

Results from the present review reveal that long-term treatment with methylphenidate might be associated with a slight growth deficit, in particular with respect to height, with a minimal clinical impact and which generally remits in adulthood. It is however possible that a clinically significant and meaningful impact may be observed on a small minority of individuals. The clinical meaning of a height deficit must be examined in the context of the advantages deriving from medication and the magnitude of the deficit: some caveat about groups of individuals who may be more severely affected is important and caution should be used in more vulnerable subjects (i.e.: the younger ones or the shortest ones with low baseline height or familiar low height as well as subjects showing a decreasing curve in height development). As specifically stated in the last NICE guidelines (2018) a planned break in treatment over school holidays should be offered if subjects' height is significantly affected by medication over time.

The impact of methylphenidate on weight is significantly less worrying, as it may change during the whole life. The limited data on pubertal maturation available at the moment seem to favour the exclusion of a possible drug effect on sexual maturation in treated ADHD subjects.

Considering the identified gaps in the current literature and the concerns form the European Medicine Agency, in 2012 the European Commission granted funding for a large research projects on long term safety of methylphenidate: the ''*Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects* " (ADDUCE; http://adhd-adduce.org). The project includes a Work Package aimed to conduct a 2-year prospective cohort study with appropriate control groups (ADHD youngsters NOT taking medications and normally developing children and adolescents) to directly address scientific questions about prevalence, clinical significance, development and moderating and/or mediating factors of four specific classes of potential long-term adverse effects of MPH (growth, neurological, psychiatric and cardiovascular health), with height velocity, as a primary outcome (Inglis et al., 2016). This large long-term study, including different control groups, should provide more suitable evidence compared to the ones currently available. It has now been completed and the results are currently being analysed for publication.

In conclusion and taking into account continuing uncertainties we do not feel that there is at the current time any evidence to suggest a need to change current clinical practice guidelines for monitoring of growth and pubertal parameters in children on stimulant medication. These all support the careful assessment of the growth parameters before starting stimulant treatment and the periodic monitoring through repeated measurement of weight and height and subsequent plotting of these on standardised growth charts. Particular caution should be taken in pre-school children where adverse effects are more likely and the final dose of methylphenidate should be achieved progressively, on the basis of the minimum effective dose for optimal treatment (Swanson et al., 2006; Graham et al., 2011; Banaschewski et al., 2006).

Disclosures

Dr. Balia had collaborations within projects from the European Union (7th Framework Program) and as sub-investigator in sponsored clinical trials by Lundbeck, Otsuka, Janssen Cilag and Angelini.

Prof. Banaschewski served in an advisory or consultancy role for Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Shire. He received conference support or speaker’s fee by Lilly, Medice, Novartis and Shire. He has been involved in clinical trials conducted by Shire & Viforpharma. He received royalities from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press. The present work is unrelated to the above grants and relationships.

Prof. Buitelaar has served as a consultant to / member of advisory board of / and/or speaker for Takeda/Shire, Roche, Medice, Vifor and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties.

Dr. Carucci had collaborations within projects from the European Union (7th Framework Program) and as sub- investigator in sponsored clinical trials by Shire Pharmaceutical Company, Lundbeck, Otsuka, Janssen Cilag and Angelini. Travel support from Fidia Farmaceutici.

Prof. Coghill served in an advisory or consultancy role for Medice, Shire/Takeda. He received conference support or speaker's fee by Servier, Medice, and Shire. He has been involved in clinical trials conducted by Shire and Tova. He received royalties from Oxford University Press. The present work is unrelated to the above grants and relationships.

Prof. Danckaerts received speaker's fees by Shire and Medice. She is involved in clinical trials conducted by Shire and received royalties form Oxford University Press. The present work is unrelated to the above grants and relationships

Prof. Dittmann has received compensation for serving as consultant or speaker, or he or the institution he works for have received research support or royalties from the organizations or companies indicated: EU (FP7 Programme), US National Institute of Mental Health (NIMH), German Federal Ministry of Health/Regulatory Agency (BMG/BfArM), German Federal Ministry of Education and Research (BMBF), German Research Foundation (DFG), Volkswagen Foundation; Boehringer Ingelheim, Ferring, Janssen-Cilag, Lilly, Lundbeck, Otsuka, Servier, Shire, Sunovion/Takeda and Theravance. He owns Eli Lilly stock.

Prof. Gagliano was in the advisory boards for Eli Lilly and Shire. She is/has been involved in clinical trials conducted by Eli Lilly, Shire, Lundbeck, Janssen and Otsuka. She has been speaker for Novartis, Eli Lilly and Shire.

Dr. Garas has no competing interests to report

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Dr Inglis has no competing interests to report

Dr. Kovshoff has no competing interests to report

Dr. Lampis served in an advisory or consultancy role for Kyowa Kirin. He received conference support or speaker's fee by Ipsen, He has been involved in clinical trials conducted by Ipsen. The present work is unrelated to the above grants and relationships.

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Dr. Panei is a consultant to the Local Health Units Rome 1 and Rome 2 of the Health Service of the Lazio region. The present work is unrelated to the above appointments.

Dr. Nagy has no competing interests to report

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Dr. Zuddas served in an advisory or consultancy role for Angelini, EduPharma, Servier. He received conference support or speaker's fee by Angelini and Janssen. He has been involved in clinical trials conducted by Angelini, Janssen, Lundbeck, Otsuka, Roche, Sevier and Shire. He received royalties from Giunti OS, Oxford University Press. The present work is unrelated to the above grants and relationships

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6 TABLES

6.1 TABLE I. CHARACTERISTICS OF THE STUDIES INCLUDED IN THE QUANTITATIVE ANALYSIS

Author, year	Study design	N ADHD [completers*] (final FU)	Gender % Male	Type of sample	Controls [completers*]	Age mean±SD [range]	Med Formulation	MPH Dose mg/d (mg/kg/d) [range]	FU length months (length of treat, m)	Primary outcome measures	Main results
Lisska &Rivkees, 2003	Retrospective	84	81	Drug naïve	87 siblings no ADHD	8.7±2.7	MPH	22.5±7.8 [5-85]	36	Height/Height velocity Z scores absolute value BMI	Effect on height in both gender, dose correlation in males
Poulton &Cowell, 2003	Retrospective	51	86.2	Drug naïve	-	7.2±1.9 [3.1-11.4]	MPH/AMP	27.5 (1.0±0.24) [10-40]	42 (23)	Height/weight/ Height velocity Z scores	Effect on height and weight after 6 and 18 months up to 30 months. Effect on height velocity during first 30 months
Bereket, 2005	Prospective	72 (14)	71.4	Drug naïve	-	8.12±1.8 [6.47-10.42]	MPH	(0.75)	16	Height/weight/BMI Z scores	No effects on height, weight and BMI by MPH treatment
Charach, 2006	Observational prospective	79 (49)	70.8	Drug naïve	-	8.3±1.5 [6-12]	MPH/AMP (IR e LA)	31.9 (0.6)	60	Height/weight Z scores	Dose related effect on height and weight. ≥ 1,5 mg/kg/day on weight 1st y ≥2,5 mg/kg/day on height in 4 y
Pliska, 2006	Retrospective Comparative	113 (42)	80.4	-	66 AMP (21)	8.5±2.1 [7-17]	MPH (IR e LA)	34.8	36 (2.6)	Height/Weight/BMI Z scores	Weight and BMI loss AMP>MPH, MPH>first 12 months. Mild correlation with cumulative dose for height
Spencer, 2006	Observational prospective	407 [178]	82.8	154 No drug naive	-	9.4±1.7 [6-13]	MPH (OROS)	34.3-43.7 (1.1-1.2)	21	Height/Weight/BMI Z scores Height/Weight/BMI Deficit Malnutrition Index	Slight height and BMI decrease during first 12 months. Slight weight loss first 5 months Effects> drug naïve, younger ss, continuous treatment
Zachor, 2006	Retrospective	81	65.4	-	-	8.5 [5-19]	MPH/AMP	-	36	Height/Weight Z scores BMI absolute values	Impact on weight> first months up to 24 months. Weight loss related to basal parameters and age (prepuberal). No impact on height in the long term

[completers*]: available growth data; **FU**: Follow up; **SD**: Standard Deviation; **ADHD**: Attention Deficit/Hyperactivity Disorder**; MPH**: Methylphenidate; **IR**: Immediate release; **LA:** Long Acting; **AMP**: amphetamine; **y:** year; **ss:** subjects

Table I. Characteristics of the studies included into the quantitative analysis

Author, year	Study design	N ADHD [completers*] (final FU)	Gender % Male	Type of sample	Controls [completers*]	Age mean±SD [range]	Med Formulation	MPH Dose mg/d (mg/kg/d) [range]	FU length months (length of treat, m)	Primary outcome measures	Main results
Faraone, 2007	Retrospective	154 [127]	-	57 Drug naïve	-	[6-12]	MPH (MTS)	[6-43.2]	36	Height/weight/BMI Z scores	Mild effect on height, weight and BMI mostly during first 12 months. Relation to dose, drug naïve condit and basal auxol parameters
Swanson, 2007	Observational prospective	485 [370]	79	88 Drug naïve *"Newly med"*	260 LNCG	[7.7-9.0]	MPH/AMP	30.3	36	Height/weight/BMI Z scores	Effect on weight and height. Relation to dose (height) and length of treat (weight and height)
Poulton, 2012	Prospective	34 (24)	85.2	Drug naïve	241 DXA at baseline	7.3±1.3 [4.7-9.1]	MPH/AMP (IR e LA)	24.3±6.2 (0.91±0.19)	36	Height/weight/BMI Z scores	Effect on weight/height/BMI > first 6 months. Bone maturation deceleration
Durà-Travè, 2012	Retrospective	187 (160)	69	-	-	8.14±1.60	MPH (OROS)	[25-55]	48	Height/weight/BMI Z scores Mean diff between expected and observed values	Effect on weight and height > first 30 months. Effect on weight from 12 moth, on height from 24 month
Germinario, 2013	Observational prospective	1758 [590] 296 MPH (90)	87.1	Drug naïve	294 ADHD on ATX	[6-18]	MPH-IR	18.8±10.7 (0.48±0.22)	24	Height/weight absolute values and percentiles Height Z score	Effect on height ATX>MPH after 12 months
Harstad, 2014	Partially retrospective	243 [171]	72.0	-	394	10.2 ±3.5	MPH/AMP	26.2±10.7	-	Height Z score Peak height velocity (PHV) Adult Height	ADHD=controls and ADHD MED= NO MED for PHV and adult height NO significant decrease on height Z score Positive relation between length of treatment and PVH in males
Powell, 2015	Observational retrospective	410	90	Drug naïve			MPH/AMP	9.2 [3.3-17.6]	>72	Height/weight Z scores	Effect on weight and height with attenuation after 12-47 months but baseline values not reached at 72+ months. Effect dose related

[completers*]: available growth data; **FU**: Follow up; **SD**: Standard Deviation; **ADHD**: Attention Deficit/Hyperactivity Disorder**; LNCG:** Local Normal Comparison Group; **MPH**: Methylphenidate; **IR**: Immediate release; **LA:** Long Acting; **MTS:** Methylphenidate Transdermal Delivery System; **AMP**: amphetamine; **y:** year; **auxol.:** auxological; **condit.**: condition

Table I. Characteristics of the studies included into the quantitative analysis

Author, year	**Study design**	**N ADHD [completers*] (final FU)**	**Gender % Male**	**Type of sample**	**Controls [completers*]**	**Age mean±SD [range]**	**Med Formulation**	**MPH Dose mg/d (mg/kg/d) [range]**	**FU length months (length of treat, m)**	**Primary outcome measures**	**Main results**
Poulton, 2016	Prospective	73 [40]	81	Drug naïve	siblings 35 [22]	7.96 ± 1.82 [4.08 - 11.61]	MPH/AMP (IR e LA)	25.5 ± 8.7 (0.87 ± 0.34)	36	Height/weight Z scores and height/weight velocity	Effect on weight and height. Effect on weight> in first 6 months. Larger doses > effects
Landgren, 2017	Retrospective Within subjects design	70	87	-		12±2.4 [8-17]	LA MPH	(0.95) [0.4-2.6]	39	Height/weight/BMI Z scores	Slight impact on height and weight. Baseline height (taller) influenced height at follow up. Larger doses>effects on weight and BMI
Diez-Suarez, 2017	Observational retrospective	342	80.13	Drug naïve	-	10.7± 3.84 [6-18]	MPH any formulation	59.7±22.9 (1.25±0.40)	27 14-41^	Height/weight/BMI Z scores	Effect on BMI and weight. Effect on height on children 6-12 Effect on height > females, younger and higher doses
Granato, 2018	Retrospective	159 [93]	78.5	93 Drug naïve	334	[5.1 -13.8]	MPH	-	30	Height/BMI Z scores	No impact on height Significant decrease in BMI

[completers*]: available growth data; **FU**: Follow up; **m**: mean; **SD**: Standard Deviation; **ADHD**: Attention Deficit/Hyperactivity Disorder; **MPH**: Methylphenidate; **IR**: Immediate release; **LA:** Long Acting; **AMP**: amphetamine

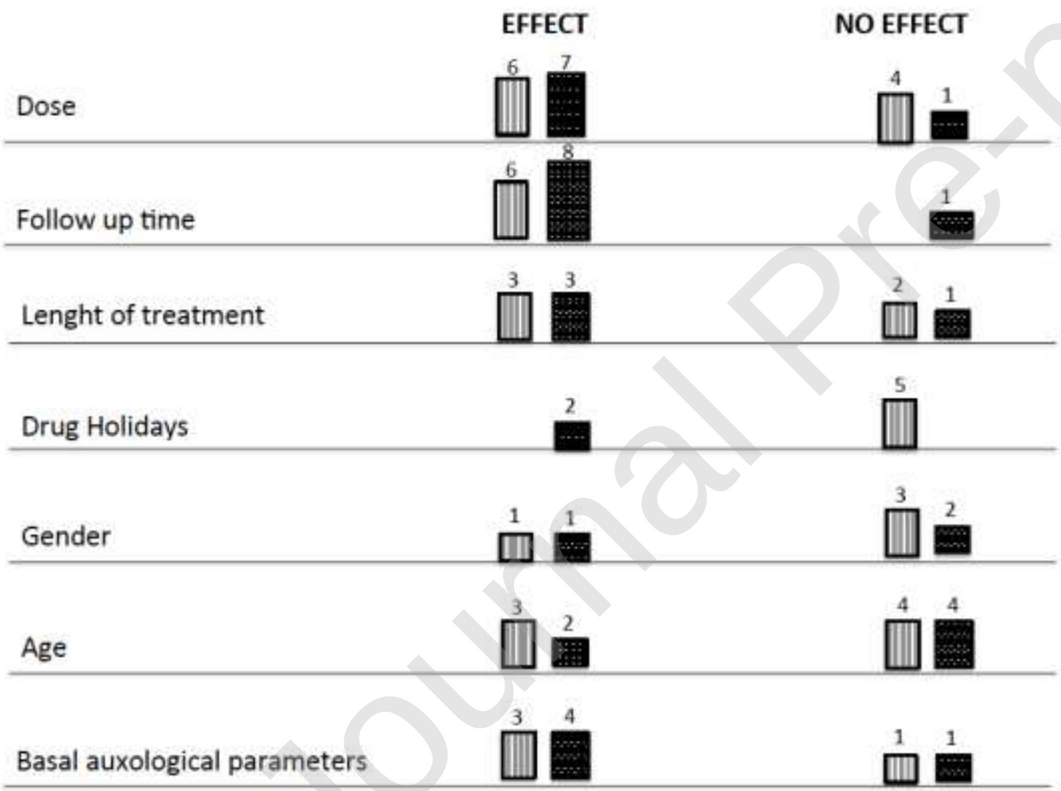
6.2 TABLE II. STUDIES EXAMINING POSSIBLE CLINICAL CORRELATES

Study	Outcome measure	N ADHD MPH	FU time		Dose		Length of treatment		Drug holidays		Drug Naïve condition		Gender		Age		Pubertal stage		Basal auxological parameters	
			H	W	H	W	H	W	H	W	H	W	H	W	H	W	H	W	H	W
Lisska, 2003	Z score	84			YES (M)				NO											
Poulton, 2003	Z score	51	YES	YES					NO											
Bekeret, 2005	Z score	72																		
Charach, 2006	Z score	49			YES	YES	YES	NO												
Pliska, 2006	Z score	113		YES	POSS		NO		NO						NO					
Spencer, 2006	Z score	178							NO	POSS	NO	YES			YES	NO			NO	NO
Zachor, 2006	Z score	81		YES												YES				YES
Faraone ,2007	Z score	127	YES	YES	NO	YES		YES			NO	YES							YES	YES
Swanson, 2007	Z score	370			YES	YES	YES	YES												
Durà-Travè, 2012	Z score	160	YES	YES	NO	NO							NO	NO	NO	NO				
Poulton, 2012	Z score	24	YES	YES																
Germinario, 2013	Z score	297	YES	YES																
Harstad, 2014	PHV	243					YES													
Diez-Suarez, 2017	Z score	342			YES	YES	POSS	YES					YES	YES	YES	NO				
Powell, 2015	Z score	410			YES	YES							NO	NO	NO	NO			YES	^
Poulton, 2016	Z score	73	YES	YES	YES	YES			NO	POSS					YES	YES				YES
Landgren, 2017	Z score Percentile	70			NO	YES	NO	-					NO	-	NO	-			YES	-
Granato, 2018	Z score	252		NO																YES

H: height; **W:** weight; **FU:** Follow Up; **M**: males; **PHV**: Peak Height Velocity; ^ = Patients with decrease in relative weight within the first 12 months experienced a more profound relative weight loss.; patients with weight loss in the first year experienced a more serious relative height deficit.

6.3 FIGURE A. HARVEST PLOT

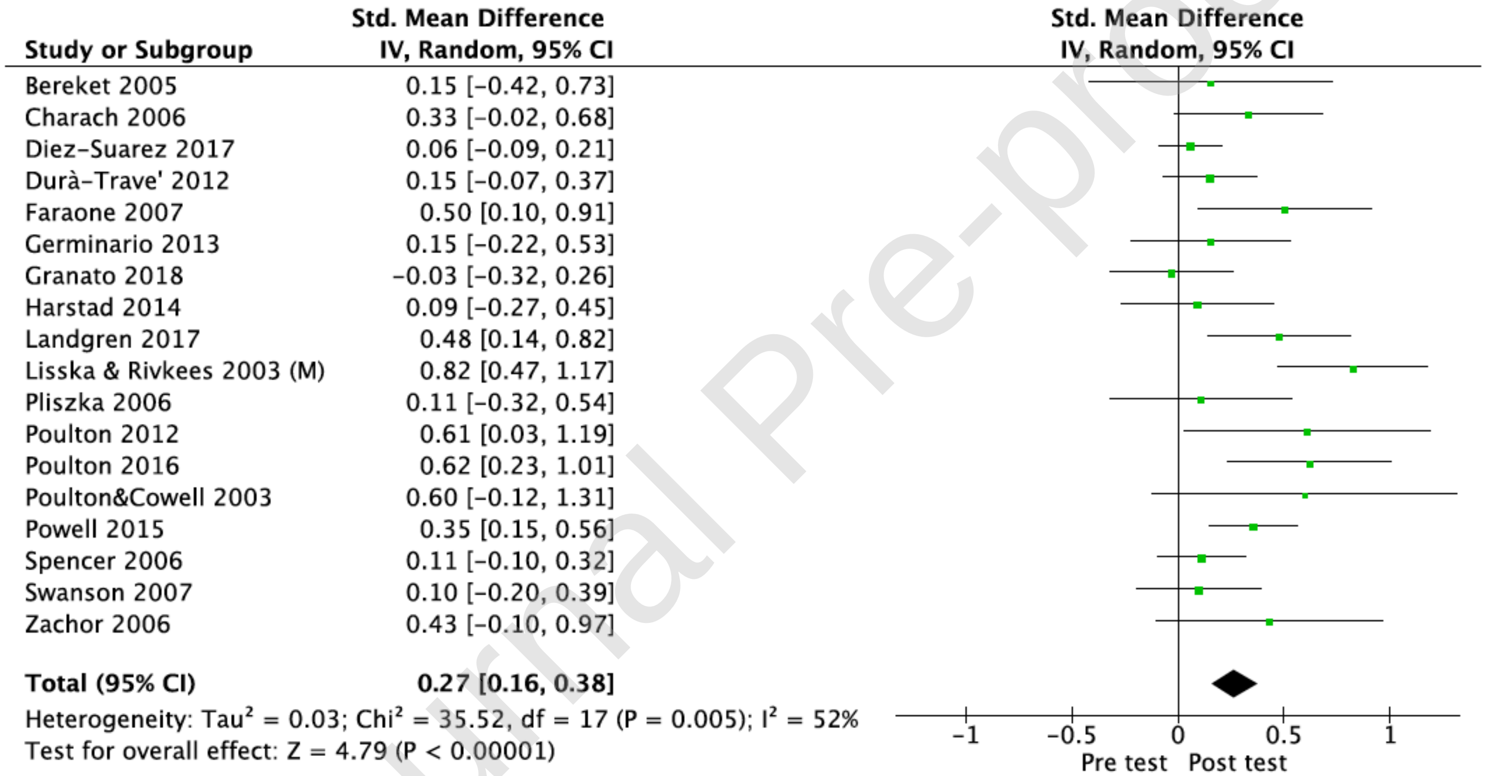
Graphical representation of possible clinical correlation within the studies. Numbers are the number of studies examining the variable expressed in the row. Width and height of the columns represent respectively the number of the studies and the total the sample size. Grey columns represents height, black stay for weight.



6.4 TABLE A. SUMMARY OF SENSITIVITY ANALYSES

Moderators of treatment effect	**Height**	**Weight**
MPH as monotherapy	YES	YES
MPH formulation	YES	YES
MPH dose	NO	NO
Subjects age	NO	NO
Drug naive condition	NO	NO
Study design (prospective vs retrospective)	NO	NO

Figure 1. Forest plot with pre-post SMD (=ES) and homogeneity statistics for meta-analysis of height (MPH and AMP).

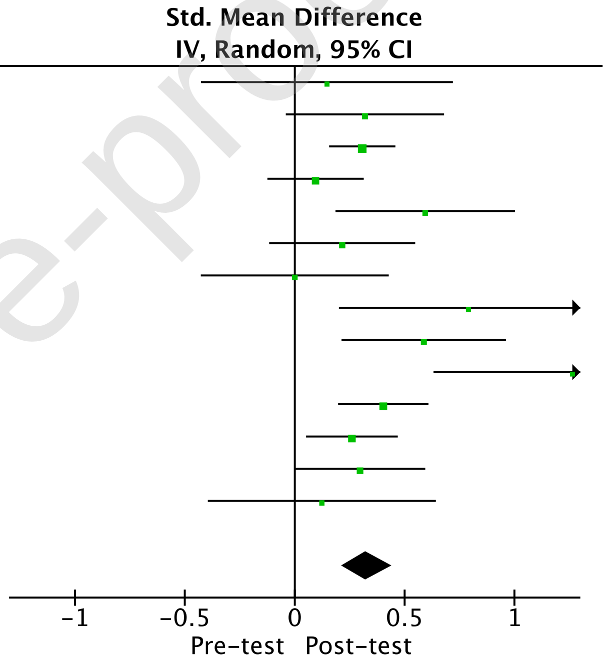


Pre–post within-group design analyses for height with stimulant therapy (methylphenidate and amphetamine, when it was not possible to distinguish between the two) at the last follow up assessment.

Figure 2. Forest plot with pre-post SMD (=ES) and homogeneity statistics for meta-analysis of weight (MPH and AMP).

Study or Subgroup	Std. Mean Difference IV, Random, 95% CI
Bereket 2005	0.15 [−0.43, 0.72]
Charach 2006	0.32 [−0.04, 0.68]
Diez−Suarez 2017	0.31 [0.16, 0.46]
Durà−Trave' 2012	0.09 [−0.12, 0.31]
Faraone 2007	0.59 [0.18, 1.00]
Landgren 2017	0.22 [−0.12, 0.55]
Pliszka 2006	0.00 [−0.43, 0.43]
Poulton 2012	0.79 [0.20, 1.38]
Poulton 2016	0.59 [0.21, 0.96]
Poulton&Cowell 2003	1.26 [0.63, 1.90]
Powell 2015	0.40 [0.20, 0.61]
Spencer 2006	0.26 [0.05, 0.47]
Swanson 2007	0.30 [−0.00, 0.59]
Zachor 2006	0.12 [−0.40, 0.64]
Total (95% CI)	**0.33 [0.22, 0.44]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 23.10$, df = 13 (P = 0.04); $I^2 = 44\%$
Test for overall effect: Z = 5.68 (P < 0.00001)

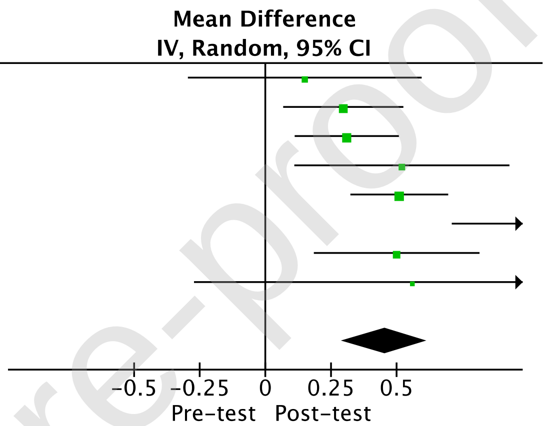


Pre–post within-group design analyses for weight with stimulant therapy (methylphenidate and amphetamine, when it was not possible to distinguish between the two) at the last follow up assessment.

Figure 3. Forest plot with pre-post SMD (=ES) and homogeneity statistics for meta-analysis of weight (MPH and AMP, 12-18 months of follow up).

Study or Subgroup	Mean Difference IV, Random, 95% CI
Bereket 2005	0.15 [−0.30, 0.60]
Charach 2006	0.30 [0.07, 0.53]
Durà−Trave' 2012	0.31 [0.11, 0.51]
Faraone 2007	0.52 [0.11, 0.93]
Poulton 2016	0.51 [0.32, 0.70]
Poulton&Cowell 2003	1.21 [0.71, 1.71]
Swanson 2007	0.50 [0.18, 0.82]
Zachor 2006	0.56 [−0.27, 1.39]
Total (95% CI)	**0.46 [0.29, 0.62]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 14.75$, df = 7 (P = 0.04); $I^2 = 53\%$
Test for overall effect: Z = 5.51 (P < 0.00001)

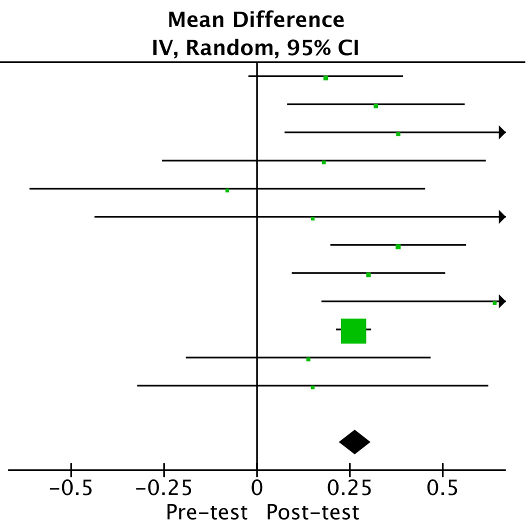


Pre–post within-group design analyses for weight with stimulant therapy (methylphenidate and amphetamine) at the 12-18 months follow up assessment.

Figure 4. Forest plot with pre-post SMD (=ES) and homogeneity statistics for meta-analysis of height (MPH and AMP, 24 months of follow up).

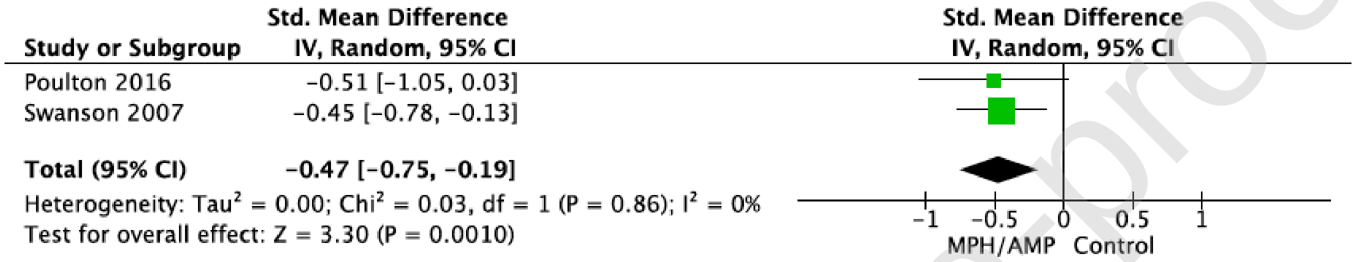
Study or Subgroup	Mean Difference IV, Random, 95% CI
Charach 2006	0.18 [−0.02, 0.39]
Durà−Trave' 2012	0.32 [0.08, 0.56]
Faraone 2007	0.38 [0.07, 0.69]
Germinario 2013	0.18 [−0.26, 0.62]
Granato 2018	−0.08 [−0.61, 0.45]
Harstad 2014	0.15 [−0.44, 0.74]
Lisska & Rivkees 2003 (M)	0.38 [0.20, 0.56]
Poulton 2016	0.30 [0.09, 0.51]
Poulton&Cowell 2003	0.64 [0.17, 1.11]
Powell 2015	0.26 [0.21, 0.31]
Swanson 2007	0.14 [−0.19, 0.47]
Zachor 2006	0.15 [−0.32, 0.62]
Total (95% CI)	**0.27 [0.22, 0.31]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.18$, df = 11 (P = 0.70); $I^2 = 0\%$
Test for overall effect: Z = 12.54 (P < 0.00001)



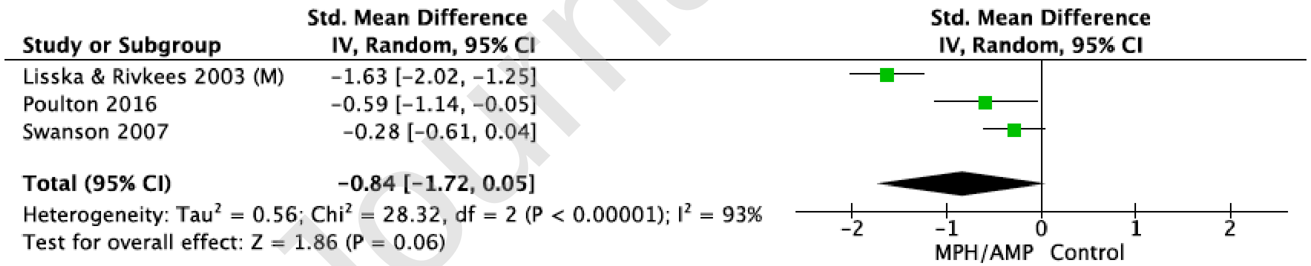
Pre–post within-group design analyses for height with stimulant therapy (methylphenidate and amphetamine) at the 24 months follow up assessment.

Figure 5. Forest plot with SMD (=ES) and homogeneity statistics for meta-analysis of weight (control trials).



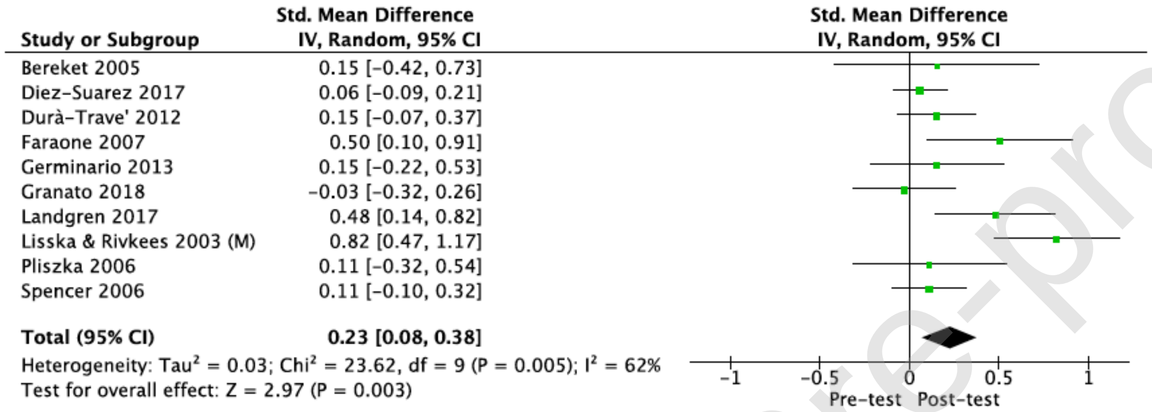
Meta-analysis of controlled trials for weight with not medicated ADHD subjects and typically developing siblings as control population

Figure 6. Forest plot with SMD (=ES) and homogeneity statistics for meta-analysis of height (control trials).



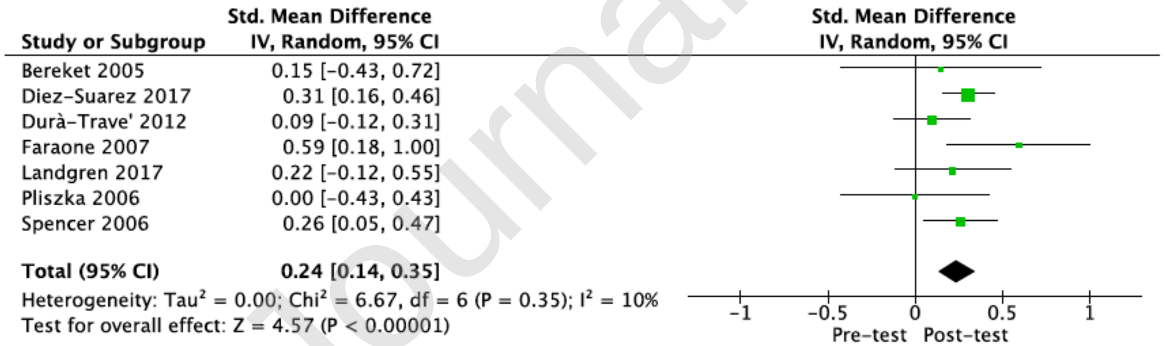
Meta-analysis of controlled trials for height with not medicated ADHD subjects and typically developing siblings as control population

Figure 7. Forest plot with pre-post SMD (=ES) and homogeneity statistics for meta-analysis of height (MPH).



Pre–post within-group design analyses for height with MPH as mono-therapy.

Figure 8. Forest plot with SMD (=ES) and homogeneity statistics for meta-analysis of weight (MPH).



Pre–post within-group design analyses for weight with MPH as mono-therapy.

Fig. 1-4 and 7-8. Forest plots with pre-post standardized mean differences SMDs (ES) and homogeneity statistics for meta-analyses of height and weight Z scores. The forest plots represent each study in the meta-analysis, plotted according to the SMD. The green box on each line shows the SMD for each study. The size of the box stands for the size of the sample size. The black diamond at the bottom of the graph shows the average SMD of all studies of all medications. If a green box or the black diamond stands on the right side of the middle line, this represents a higher Z score on the pre-test in comparison with the post-test, so a decrease. A box/diamond on the left side of the middle line represents a higher Z score on the post-test in comparison with the pre-test, so an increase. If the green box or the black diamond crosses the middle line, then this study reported no significant effect.

Fig. 5,6. Forest plots with standardized mean differences SMDs (ES) and homogeneity statistics for meta-analyses of height and weight Z scores in controlled trials. If a green box or the black diamond stands on the right side of the middle line, this represents a lower Z score for the medicated subjects compared to the control population at the latest follow up time.

6.5 APPENDIX 1

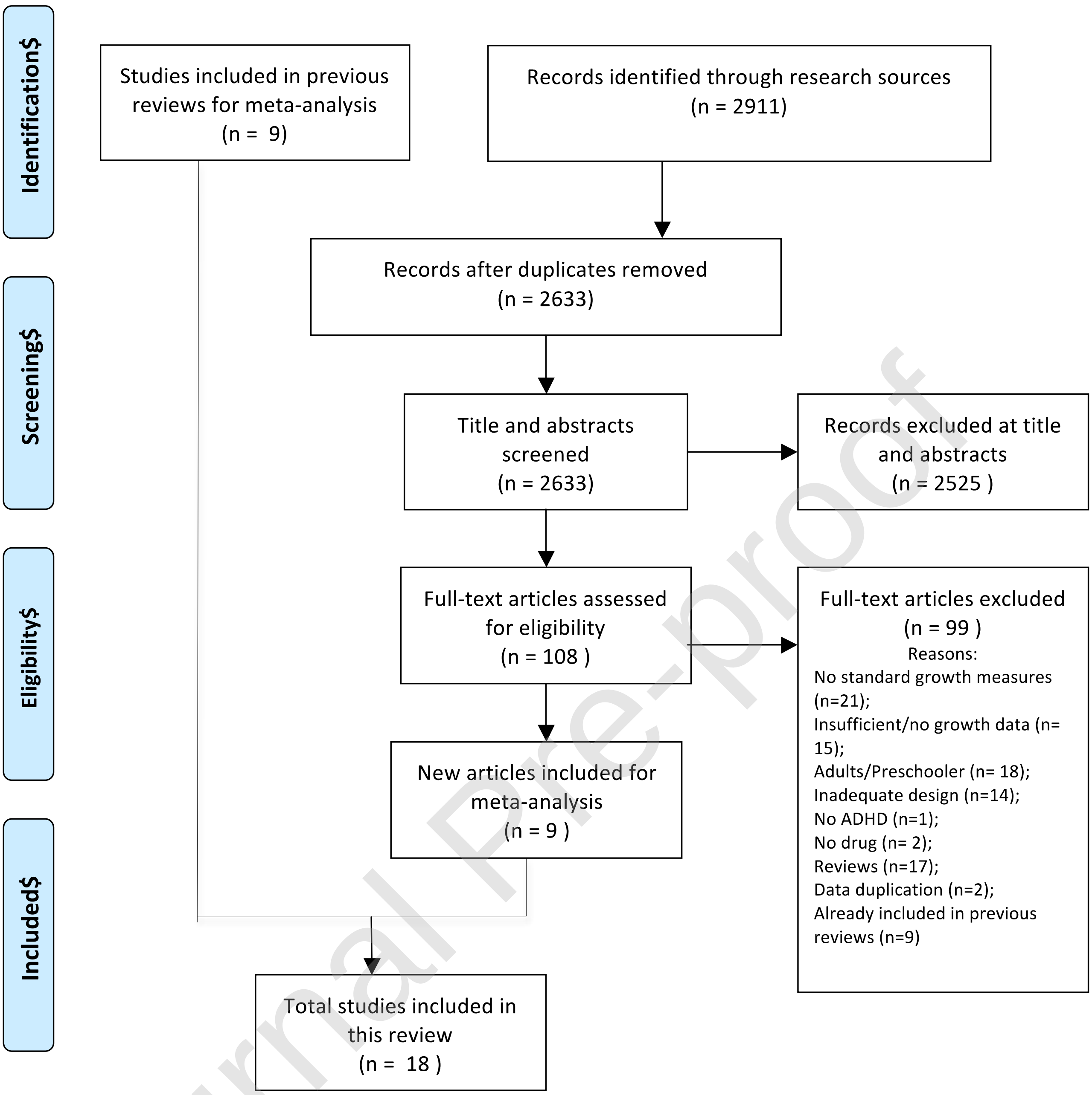
Medical subject headings [MeSH] and terms as free text word used for the search

"MPH": *Methylphenidate OR methylphenidate hydrochloride OR methylphenidate hcl OR metadata* OR *Medikinet OR methylin OR Ritalin OR equasym OR daytrana OR concerta*

"Side effects": *adverse effects OR adverse reaction OR adverse reactions OR side effect OR side effects OR untoward effect OR untoward effects OR adverse drug experience OR adverse drug experiences OR adverse drug reaction OR adverse drug reactions OR drug experience report OR drug experience reports OR toxic reaction OR toxic reactions OR toxic effect OR toxic effects OR complication OR complications OR undesired effect OR undesired effects OR unwanted drug effect OR unwanted drug effects OR "drug toxicity" OR "adverse drug reaction" OR "unwanted drug effects"*

"ADHD": *hyperkinetic syndrome OR hyperactivity disorder OR hyperactive child syndrome OR childhood hyperkinetic syndrome OR attention deficit hyperactivity disorders OR attention deficit hyperactivity disorder OR adhd attention deficit hyperactivity disorder OR addh OR overactive child syndrome OR attention deficit hyperkinetic disorder OR hyperkinetic disorder OR adhd OR attention deficit disorder hyperactivity OR attention deficit disorders hyperactivity OR child attention deficit disorder OR hyperkinetic syndrome OR syndromes hyperkinetic OR hyperkinetic syndrome childhood*

"Growth"*: "growth velocity" OR "growth spurt*: *AND "height " or "stature"*: *AND "adult height" OR "adult stature" OR definitive stature".*



Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA[a]) flow diagram on growth effects.
aPRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses (http://www.prisma-statement. org).